

Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial

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Objective: To ascertain whether therapeutic equivalence exists for the treatment of paediatric community acquired pneumonia by the oral and intravenous (IV) routes.

Methods: A multicentre pragmatic randomised controlled non-blinded equivalence trial was undertaken in eight paediatric centres in England (district general and tertiary hospitals). Equivalence was defined as no more than a 20% difference between treatments of the proportion meeting the primary outcome measure at any time. 246 children who required admission to hospital and had fever, respiratory symptoms or signs and radiologically confirmed pneumonia were included in the study. Exclusion criteria were wheeze, oxygen saturations <85% in air, shock requiring >20 ml/kg fluid resuscitation, immunodeficiency, pleural effusion at presentation requiring drainage, chronic lung condition (excluding asthma), penicillin allergy and age <6 months. The patients were randomised to receive oral amoxicillin for 7 days (n=126) or IV benzyl penicillin (n=120). Children in the IV group were changed to oral amoxicillin after a median of six IV doses and received 7 days of antibiotics in total. The predefined primary outcome measure was time for the temperature to be <38°C for 24 continuous hours and oxygen requirement to cease. Secondary outcomes were time in hospital, complications, duration of oxygen requirement and time to resolution of illness.

Results: Oral amoxicillin and IV benzyl penicillin were shown to be equivalent. Median time for temperature to settle was 1.3 days in both groups (p<0.001 for equivalence). Three children in the oral group were changed to IV antibiotics and seven children in the IV group were changed to different IV antibiotics. Median time to complete resolution of symptoms was 9 days in both groups.

Conclusion: Oral amoxicillin is effective for most children admitted to hospital with pneumonia (all but those with the most severe disease who were excluded from this study). Prior to this study, the British Thoracic Society guidelines on childhood pneumonia could not draw on evidence to address this issue. This will spare children and their families the trauma and pain of cannulation, and children will spend less time in hospital.

Pneumonia is a common paediatric illness with 2.5 million cases annually in Europe,¹ most commonly in children aged <5 years (incidence 21–36/1000 in the developed world).^{2–3} Around 40% of cases require hospitalisation.^{2–3} The clinician has to make management decisions regarding choice of antibiotic and mode of administration. The British Thoracic Society (BTS) guidelines for treatment of community acquired pneumonia in children⁴ made a consensus recommendation regarding the use of intravenous (IV) antibiotics for those admitted to hospital, but this was not based on evidence. It is not possible to differentiate between viral and bacterial pneumonia by chest radiography or inflammatory markers,^{5–6} so the clinician has to treat this group of children empirically with antibiotics.

There have been no randomised controlled trials in the developed world comparing administration of antibiotics by the oral and IV route for children unwell enough to require hospital admission. A study of pneumonia in children presenting to 13 hospitals in the north of England⁷ showed that the majority are admitted (89% of 711 children) and 96% received antibiotics, 70% by the IV route. The percentage of children classed as having mild, moderate and severe pneumonia was 22%, 19% and 59%, respectively, in this study.

A study was undertaken to ascertain whether therapeutic equivalence exists for treatment of community acquired pneumonia by the oral and IV route. Since oral antibiotics are

cheaper and more acceptable to families and clinicians, being a less painful and non-invasive treatment, an equivalence trial was deemed the most appropriate approach to this question as there is no need to demonstrate superiority.

METHODS

Patients

The study was a multicentre randomised but non-blinded equivalence trial of oral versus IV treatment for pneumonia in previously well children. Children were recruited from eight centres in England (Queen's Medical Centre, Nottingham; City Hospital, Nottingham; Derby Children's Hospital, Derby; King's Mill Hospital, Mansfield; Lincoln County Hospital, Lincoln; Heartlands Hospital, Birmingham; New Cross Hospital Wolverhampton; and University Hospital North Staffordshire). All children admitted to hospital with pneumonia were eligible. Three inclusion criteria had to be met for pneumonia to be diagnosed: respiratory symptoms or signs, temperature $\geq 37.5^{\circ}\text{C}$ or a history of fever at home, and a radiological diagnosis of pneumonia (defined as a confluent area of consolidation agreed subsequently by two independent radiologists). The decision to admit and study eligibility was assessed by the admitting team. Exclusion criteria were wheeze, oxygen saturations <85% in air, shock requiring >20 ml/kg

Table 1 Demographic data and clinical variables (per protocol analysis)

Variable	Oral treatment (N = 100)	IV treatment (N = 103)
Sex, n (%) male	53 (53%)	55 (53%)
Age (years)*	2.4 (1.5–5.4)	2.5 (1.4–4.7)
Number of children treated with oral antibiotics pre-admission	18 (18%)	14 (13.6%)
Number of days of treatment with antibiotics pre-admission*		
<2	14/18 (78%)	12/14 (86%)
2–5	0/18	2/14 (14%)
>5	4/18 (22%)	0/18
Length of illness pre-admission in days‡	5 (2.5–7.0)	4.5 (2.0–7.0)
Admission observations†		
Temperature (°C)	38.6 (38.4 to 38.8)	38.4 (38.2 to 38.6)
Pulse	151 (146 to 156)	149 (144 to 153)
Respiratory rate		
<1 year	50 (45 to 61)	50 (45 to 61)
>1 year	40 (37 to 43)	43 (40 to 46)
Oxygen saturation (in air)	95% (94 to 96)	95% (95 to 96)
Symptoms and signs on admission		
Cough	89 (89%)	95 (92%)
Recession	42 (42%)	51 (49.5%)
Grunting	14 (14%)	25 (24%)
Difficulty breathing	34 (34%)	33 (32%)
Investigations		
Blood taken from	79/100 (79%)	89/103 (86%)
Throat swab or NPA taken from	55/100 (55%)	52/103 (50%)
White cell count ($\times 10^9/l$)†	19 (16.8 to 20.8)	18 (16.5 to 19.6)
Neutrophil count ($\times 10^9/l$)†	14 (12.3 to 15.9)	13.4 (11.9 to 14.9)
CRP (mg/l)†	159 (128 to 190)	172 (144 to 199)
Blood culture	1 positive (<i>Streptococcus pneumoniae</i>)	3 positive (<i>Streptococcus pneumoniae</i>)
Viral throat swab or NPA	Positive 7/54 (13%)	Positive 7/52 (13%)
	4 RSV	5 RSV
	2 influenzae A	1 influenzae A
	1 adenovirus	1 parainfluenzae

CRP, C-reactive protein; NPA, nasopharyngeal aspirate; RSV, respiratory syncytial aspirate.

No significant difference was seen between the two groups in white cell count, neutrophils or CRP.

*The oral antibiotics given prior to hospital admission included amoxicillin (11), cephalixin (2), co-amoxiclav (3), penicillin (4), erythromycin (7), clarithromycin (1) and trimethoprim (4).

†Mean (95% confidence interval).

‡Median and 25th–75th centile.

fluid resuscitation, immunodeficiency, pleural effusion at presentation requiring drainage, chronic lung condition (excluding asthma), penicillin allergy and age <6 months. Treatment with oral antibiotics in the 5 days prior to admission, including amoxicillin, was not an exclusion criterion.

Procedure

Written informed consent was obtained before randomisation. A block randomisation sequence stratified by centre was produced using a random number generator. The sequence was accessed via the internet, therefore allowing concealment of allocation. Children were randomly assigned to oral amoxicillin (chosen in preference to oral penicillin owing to the superior absorption⁸ and palatability) or IV benzyl penicillin. Children in the IV group were changed to oral amoxicillin on discharge or sooner if the clinical team considered their improvement warranted this. Both groups completed a 1-week course of antibiotics in total. Doses were taken from *Medicines for Children* (2001),⁹ the most authoritative guide to paediatric drug doses at the time in the UK. Oral amoxicillin: 6 months to 12 years, 8 mg/kg three times a day; 12–16 years, 500 mg three times a day. Benzyl penicillin IV: 6 months to 16 years, 25 mg/kg four times a day.

Admission investigations included, full blood count, C-reactive protein, blood culture and a viral throat swab or nasopharyngeal aspirate (for viral immunofluorescence and culture for respiratory syncytial virus, adenovirus, parainfluenzae and influenza A and B viruses). The protocol included as rescue treatment, in addition to amoxicillin or benzyl penicillin, oral erythromycin (in both treatment groups) or clarithromycin IV if oral medication was not tolerated. This was started at 48 h if no clinical improvement

was noted. Parents were telephoned 2 weeks following discharge and weekly thereafter until the child was judged by the parent to be back to normal (defined as not coughing more than before the pneumonic illness and energy levels back to normal).

Outcome measures

The primary outcome measure was time from randomisation until the temperature was <38°C for 24 continuous hours and oxygen requirement had ceased (the latter only applicable to those children who required oxygen during the admission). It can be seen from the inclusion criteria that a temperature of >37.5°C was chosen although the primary outcome measure is based on a temperature of <38°C. Many children would have been treated with antipyretics before presentation to hospital and therefore using a higher cut-off point would have unnecessarily excluded a proportion of children with pneumonia. The use of a temperature <38°C for recovery was decided by a consensus group of senior clinicians before the start of the study. Secondary outcomes included time in hospital, complications (empyema, readmission, further courses of antibiotics), duration of oxygen requirement and time to resolution of illness. This was a pragmatic trial and the decision to change from IV to oral antibiotics and discharge home were at the discretion of the clinical team (ensuring children were not kept in hospital for longer than they would be in normal clinical practice).

Power calculation

With a 5% level of significance, 80% power and equivalence defined as no more than a 20% difference between treatments

of the proportion meeting the primary outcome measure at any time, 98 children were required in each arm of the trial. The steering group and a focus group advised that a difference of more than 20% could not be considered clinically equivalent.

Statistical analysis

Since this was an equivalence trial, the primary analysis was per protocol. Criteria for inclusion in the per protocol analysis were as follows: oral amoxicillin \pm rescue treatment for the oral group; for the IV group the child had to have received at least one dose of IV benzyl penicillin. This was a pragmatic trial and some children left hospital before the primary outcome measure was met, giving rise to censored data. Censored observations are observations for which, at the end of the study, the event of interest (time for temperature to fall to $<38^{\circ}\text{C}$ for 24 continuous hours and oxygen requirement to cease) has not occurred. There was a further small group of children (13/203 = 6%) with censored observations in whom the temperature did not go above 38°C in hospital. Survival analysis is the most appropriate technique to analyse this type of data.¹⁰ Wellek's log rank test was used to analyse for equivalence¹¹ (SAS Package Version 8.2). Therefore, for the primary outcome measure, p values of <0.05 define equivalence. Equivalence was judged as a difference of no more than 20% between the proportions of children in the two treatment groups meeting the primary outcome measure. A p value of <0.05 therefore indicates that there is no more than a 20% difference between the two treatments at any time. Other p values are for superiority. As these are multicentre data, a stratified analysis was carried out.

A second analysis of the primary outcome measure is also presented. This analysis assumes the primary outcome measure was met following discharge e.g. if a child was discharged after having a temperature of $<38^{\circ}\text{C}$ for 18 h, the primary outcome measure was assumed to have been met a further 6 h following discharge making a total of 24 h (provided the child did not re-present to hospital and the symptoms were fully resolved at telephone follow-up). Categorical data were analysed using a χ^2 test. Continuous data were analysed using a t test or Mann-Whitney U test, depending on the normality of the data. Skewed data are presented as medians with 25th and 75th centiles. A data monitoring committee met half way through the trial to monitor adverse events and trial progress.

RESULTS

Between September 2002 and June 2004, 252 children were randomised. The number of children who were eligible,

randomised, excluded and analysed in the per protocol group are shown in the online figure available at <http://thorax.bmj.com/supplemental>. Demographic variables are shown in table 1.

Primary outcome measure

For the primary outcome measure, all p values are for equivalence. Therefore, a p value of <0.05 indicates that the null hypothesis (a difference of $>20\%$ exists between the two treatments) has been disproved. As shown by the survival curves in fig 1, the time for temperature to settle and oxygen requirement to cease for those needing oxygen was similar in the two groups ($p=0.03$ for equivalence, median time 1.3 days (25th–75th centile 1.1–1.7 days) and 1.2 days (25th–75th centile 0.9–1.6 days) in the IV and oral groups, respectively). We also calculated the mean difference in the primary outcome measure between the IV and oral groups and this was found to be 0.3 h (95% confidence interval 0.21 to 0.40). Figure 2 shows the same curves using the estimated time for temperature to settle in those children who were discharged before the primary outcome measure was met. Stronger evidence of equivalence was demonstrated ($p=0.001$, median time for temperature to settle 1.3 days in both groups).

A secondary analysis of the primary outcome measure was undertaken using only time for temperature to settle and excluding oxygen requirement. The median time for temperature to be $<38^{\circ}\text{C}$ for 24 continuous hours was 1.23 and 1.3 days, respectively, in the IV and oral groups ($p<0.001$ for the per protocol analysis).

Time in hospital and oxygen requirement

The median length of hospital stay was significantly shorter in the oral group than in the IV group (1.77 days (25th–75th centile 1.2–2.0) and 2.1 days (25th–75th centile 1.8–2.9), respectively, $p<0.001$). We also calculated the median of the differences and this was found to be 0.60 days (0.15–1.13) (IV–oral). During admission, 18/103 children (17.5%) in the IV group and 28/100 children (28%) in the oral group required oxygen ($p=0.07$). The duration of oxygen requirement was significantly longer in the IV group than in the oral group (median 20.5 vs 11.0 hours, $p=0.04$). Children randomised to IV treatment received a median of 6 doses (25th–75th centile 4.7–7.5) of IV benzyl penicillin before conversion to oral amoxicillin.

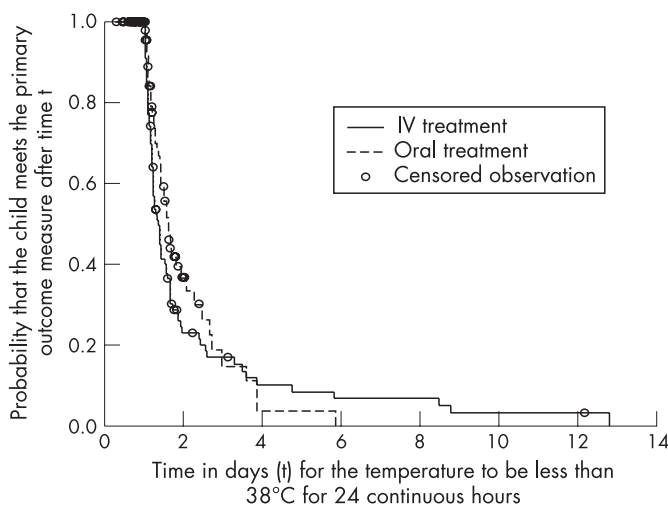


Figure 1 Survival curve for the time for the temperature to be $<38^{\circ}\text{C}$ for 24 continuous hours and oxygen requirement to cease in the two treatment groups (censored data, per protocol analysis); $p=0.031$.

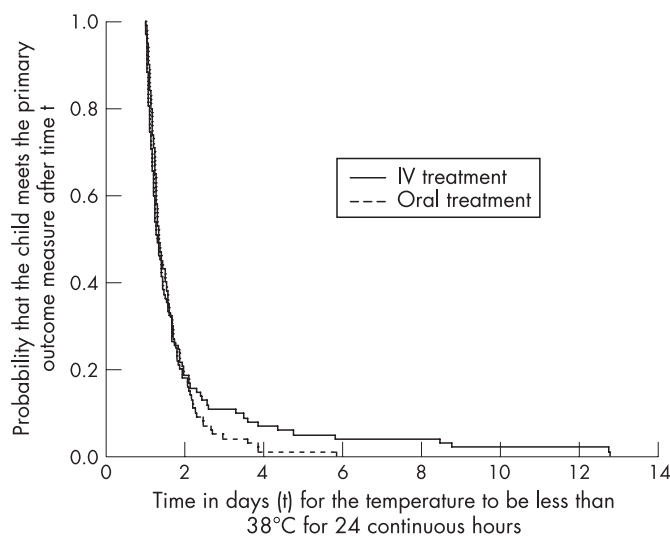


Figure 2 Survival curve for the time for the temperature to be $<38^{\circ}\text{C}$ for 24 continuous hours and oxygen requirement to cease in the two treatment groups (no censored data, per protocol analysis); $p=0.001$.

Table 2 Protocol deviations and complications

Group		Oral group (n = 126)	Intravenous group (n = 120)
A	Did not receive treatment per protocol	5 (see online figure)	4 (see online figure)
B	Received treatment per protocol but subsequently changed to a second antibiotic other than rescue treatment	3	7
C	Rescue treatment per protocol	6	8
D	Number of children in group B who were also in group C	1	6
E	Empyema requiring drainage	0	3
F	Further course of antibiotics following discharge	6	3

Protocol deviations and other antibiotic changes

Deviations from the protocol and complications are shown in table 2.

Oral group

Three children in the oral group (aged 7 months, 15 months and 3 years) commenced oral amoxicillin and were subsequently changed to IV antibiotics (benzyl penicillin or cefuroxime) because of increasing respiratory distress or oxygen requirement. One had Downs syndrome and one was subsequently diagnosed with measles.

IV group

Seven children in the IV group were changed to other IV antibiotics owing to ongoing fever. Three developed empyema (see below) and four had antibiotic changes (IV cefuroxime, ceftriaxone or cefotaxime) because of ongoing fever and worsening consolidation on chest radiography.

Empyema

Three previously healthy children, all in the IV group, aged 11 months to 2 years developed empyema requiring drainage. None had received antibiotics prior to admission. Fully sensitive *Streptococcus pneumoniae* was isolated from two of these children. In the third, no organism was identified. All made a full recovery.

Follow-up

Median time to resolution of symptoms (defined as not coughing more than before the pneumonic illness and energy levels back to normal) was 9 days in both treatment groups. Eight children received a further course of oral antibiotics for ongoing cough 5–28 days after discharge (six in the oral group and two in the IV group). All subsequently made a full recovery. One child in the IV group was readmitted to hospital 15 days after discharge with ongoing cough and new fever and received a second course of IV antibiotics.

DISCUSSION

This is the first randomised controlled trial in children in the developed world to study oral versus IV treatment for children with radiologically confirmed pneumonia treated in hospital. Our data show that oral amoxicillin and IV benzyl penicillin have equivalent efficacy for the treatment of pneumonia in previously well children. Oral treatment allowed children to go home sooner and avoided pain from cannulation. Both groups took a median of 9 days to recover.

Oral amoxicillin was chosen in preference to oral penicillin for a number of reasons. This was a pragmatic trial; most clinicians would choose amoxicillin over penicillin by the oral route because of its superior absorption and palatability.⁸

Amoxicillin does have cover against *Haemophilus* which penicillin lacks. However, since the introduction of *Haemophilus influenzae* type b vaccine, this has become a rare cause of pneumonia. Non-typable *Haemophilus* strains have never figured highly in aetiology studies.^{12–13}

Children in the IV group received oxygen therapy for a significantly longer period than those on oral treatment. Theoretically, by chance, those randomly allocated to IV treatment could have been a group of children with more severe pneumonia. However, the demographic variables suggest the groups were similar (table 1). A more likely explanation is the fact that they stayed in hospital for a longer period of time and so continued to have oxygen saturation monitoring. This may have biased the primary outcome measure towards the oral group. However, a secondary analysis of the primary outcome measure looking solely at time for temperature to settle also demonstrated equivalence.

In terms of complications, the three cases of empyema were all in children on IV therapy. Six children in the oral group and two children in the IV group received further courses of antibiotics following discharge. However, of the six children in the oral group, two had sought further advice from the GP due to ongoing cough and the other four children visited the GP with an increasing cough plus new coryza ± new fever.

Yield from blood culture at presentation was low, as seen in other studies,^{12–15} and did not predict complications. Numerous studies have shown that the white cell count and C-reactive protein levels cannot be used to differentiate between viral and bacterial pneumonia.^{6–12} These investigations did not appear to influence management decisions in this study.

There have been no studies in the developed world comparing oral and IV treatment for children with pneumonia. One study compared oral amoxicillin with a single dose of intramuscular penicillin and found no difference between the two groups.¹⁶ However, this study enrolled children well enough to be treated as outpatients so this was potentially a different population from the one in the present study. Moreover, intramuscular penicillin is not used for children in the UK and follow-up was only for 36 h. Oral amoxicillin has been claimed to be effective for the treatment of “severe pneumonia” in the developing world, but the cases were not radiologically confirmed.^{17–18} This may have led to recruitment of children with non-pneumonic respiratory illness. In contrast, our study was not stratified by disease severity but does have the major advantage that all cases analysed per protocol had radiological changes confirmed by two independent masked consultant radiologists. The study by Addo-Yabo *et al*¹⁷ demonstrated equivalence between oral amoxicillin and intramuscular penicillin for children with a clinical diagnosis of severe pneumonia (treatment failures were 19% in each group). This study is unlikely to change practice in the developed world because of a number of differences between the two populations, notably different antibiotic resistance patterns and immunisation rates and the co-existence of other disease such as malaria, HIV and malnutrition. In an era of evidence-based medicine, clinicians demand evidence that is directly applicable to the population of patients they treat. Hence studies from both the developing and developed world are needed.

A double-blind randomised controlled trial would have been the gold standard for this study. However, it would not have been acceptable to cannulate half the children to receive only placebo and frequently recannulate them if IV access was lost before the child was discharged. The pragmatic nature of the study led to a number of children being discharged before the primary outcome measure was met. It would not have been ethical to keep children in hospital for a minimum period for the purposes of the study. It was also our aim to compare oral

treatment with current IV practice, not a minimum number of doses specified for the purposes of the study. Time in hospital could have been used as the main outcome measure and would have been available for all participants but could have been biased by factors such as social circumstances, bed pressures and clinicians with different criteria for discharging children. As this was a pragmatic study, admission criteria were not applied and admission was at the discretion of the admitting team.

This study did not aim to look at aetiology which has been well documented in other studies.^{6–12} The investigations in table 1 were baseline investigations, routinely carried out on children with pneumonia admitted to hospital in the participating centres. Children in whom a virus was isolated were not excluded, as many will represent a mixed infection¹⁹ and all presented with consolidation. In this situation, the clinician would initiate and continue to treat with antibiotics. Despite the exclusion of wheezy children, it is accepted that some of the children in the study would have had viral pneumonia. It can be seen from the number of positive viral swabs that the numbers are small and, more importantly, were balanced between the two groups.

Implications for future practice

The hospitals that took part in this trial represent a mixture of small and large district general hospitals and tertiary referral centres. There is no reason to believe that they admit a different population of children with pneumonia than other hospitals in the UK. Clinical coding demonstrated that admissions for children with pneumonia did not change during the trial period, suggesting stable admission practices.

We suggest that, in countries like the UK with universal *Haemophilus influenzae* type b immunisation coverage and low rates of tuberculosis, all but the sickest children with pneumonia (ie, those meeting our exclusion criteria) should be treated with oral amoxicillin. It is expected that the majority of children will still require hospital admission, but for a shorter period to ensure oral medication is tolerated and temperature and respiratory distress are settling. Most importantly, children will be spared the pain and distress which cannulation causes—not only to them but also to their parents.

In conclusion, oral amoxicillin is likely to be equivalent in the measured clinical outcomes to intravenous penicillin for the treatment of non-severe radiographic pneumonia in children admitted to hospitals in the UK. This non-blinded randomised controlled pragmatic equivalence trial addresses an evidence gap in the BTS guidelines for treatment of community acquired pneumonia in children.⁴ Children will benefit from receiving a painless non-invasive treatment. Although not reported in this study, there are also implications for reducing the direct and indirect costs of treating pneumonia in this population.

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Further details are shown in the figure available online only at <http://thorax.bmj.com/supplemental>.

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